ISSUE SUMMARY
TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES
ADVISORY COMMITTEE MEETING
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Informational Presentation #5: Labeling Claims for TSE Clearance Studies for Plasma Derivative Products

Background

On February 20, 2003, the TSEAC voted that FDA should consider labeling claims for TSE clearance where manufacturers have undertaken clearance studies using viral-validation style methods and model TSE spiking agents. Published studies have shown that TSE clearance is not "generic," but rather depends upon the details of process, including pH, ionic strength, alcohol concentration, and the protein matrix of manufacturing intermediates. TSE clearance labeling submissions are encouraged so that FDA can receive detailed, evaluable experimental data about specific products, that would permit estimates of the ability of processing steps to clear infectivity. Labeling also provides the public with additional risk-related information. Since February 2003, FDA has received submissions from industry that contain detailed experimental TSE clearance data for specific manufacturing processes and products.

FDA outlined contents for such submissions at the TSE Advisory Committee on February 20th, 2003:

- ?? Characterization and titration of spiking agent
- ?? Accurately scaled-down processes (including use of actual production intermediates)
- ?? Robust and reproducible experiments
- ?? Well-characterized assay for TSE infectivity
  –Bridging binding assays to bioassays where relevant
- ?? Estimated logs clearance of TSE by processing steps (reduction factor and clearance factor)
- ?? Demonstration of mass balance
- ?? Demonstration, where relevant, that non- orthogonal (similar) clearance steps are/are not additive

In evaluating TSE clearance submissions, FDA has also considered:

- ?? The phenomena of "conditioning," where some steps might significantly alter the context or physical state of TSE-agent-containing material (e.g., solvent-detergent treatment), possibly affecting removal by a subsequent step.
- ?? Rationale for use of specific animal models
- ?? Rationale for use of specific spiking preparation

- Use of bioassays to confirm clearance in critical steps and/or correlation of bioassay with prion binding assays if the latter are used to assess TSE clearance

Caveats to all TSE clearance studies include imperfect knowledge about the physical form of TSE infectivity in blood and plasma, as well as the very low titer of blood/plasma infectivity (1-2 logs based upon animal models). Animal models must be used because materials and reagents for modeling of human disease are in limited supply.

Current TSE labeling (all blood products):

Product labeling communicates benefits and risks. Risk has two dimensions, first, what is the likelihood of risk, and second, what is the potential magnitude of risk. In 1999, FDA recommended labeling to communicate the possibility of TSE transmission risk from plasma derivatives. The following recommended statement is contained in the WARNINGS section of package inserts for plasma derivatives:

- "Because this product is made from human blood, it carries a risk of transmitting infectious agents, e.g. viruses, and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent."

This statement *remains on all package inserts regardless of TSE clearance claims*.

New TSE Clearance Labeling (approved)

The new labeling for products that have demonstrable, evaluated TSE clearance is contained in the DESCRIPTION section of package inserts, which is the same section that includes viral clearance studies.

The labeling states that studies were accomplished, and introduce the concept that a model agent was used. The second statement specifies the amount of TSE clearance experimentally achieved, and communicates a level of assurance when clearance is considered relative to the amount of possible TSE infectivity in starting material.

- Under DESCRIPTION: "Additionally, the manufacturing process was investigated for its capacity to decrease the infectivity of an experimental agent of transmissible spongiform encephalopathy (TSE), considered as a model for the vCJD and CJD agents."

- Under DESCRIPTION: "Several of the individual production steps in the [product name] manufacturing process have been shown to decrease TSE infectivity of an experimental model agent. TSE reduction steps include [process] [logs], [process] [logs], etc. These studies provide reasonable assurance that low levels of CJD/vCJD agent infectivity, if present in the starting material, would be removed.

Current Considerations in the Context of New Risk Information

Since FDA announced that submissions regarding TSE clearance in manufacturing would be evaluated, presumptive vCJD transmission by blood has occurred twice in the U.K., indicating that transmission by blood in humans is no longer a "theoretical" possibility. Additionally, the risk from vCJD by transfusion appears to be higher than had been expected from epidemiological studies of CJD based on the rate of infections (2 out of 18 cases) in recipients of blood from donors who later developed vCJD. To date, transmission of vCJD has not been associated with receipt of any plasma derivative. Nevertheless, in consideration of the potential risk from plasma derivatives, the U.K. has announced that recipients of coagulation factors and of IGIV will be notified if they received products manufactured from plasma of a donor that developed vCJD.

Submission of TSE clearance data to FDA for evaluation is optional, and the data received by FDA are not comprehensive across all products and manufacturers. FDA recognizes that the risk may be different for different products, and is reexamining whether TSE clearance is likely to be adequate in specific cases, given the safeguards that presently are in place.